then it doesn't matter how you distribute people by sites.

The other three curves, just to save time, the bottom one here assumes a correlation of .05. That's small. That's assuming that 5 percent of the total variation in outcomes is accounted for by variation between sites.

So even with that minimal amount of correlation, notice how much bigger the standard deviation is. I apologize that the scale on this isn't better, but that's twice as high. It's approximately twice as high as your analysis ignoring correlation says that it should be.

Incidentally, we were about here yesterday. We had five sites yesterday, and I think two of them accounted for more than 50 percent of the data.

The one point is that I would encourage going to more sites than no more than allowing any one to be up to a quarter of the data, but the second point is that if we were just talking about eyes within people, it would be straightforward to do this calculation and just account for it in calculating power and doing the analyses and what have you.

DR. WEISS: Thank you very much.

I'm going to ask Donna Lochner to speak with us a little bit more about this issue.

MS. LOCHNER: Well, I think this is helpful,

but the kind of recommendation we need clinically is what factors do we base the correlation on and what is the correlation that would be plugged prospectively, as you're stating, into this equation?

DR. WEISS: And I should also add with information from you already is the precedence to date, is that LASIK is a little unusual because each eye has been considered a separate entity, but the history has basically been for intraocular lenses one patient, whether or not they had both eyes done or one done, was a separate entity. Viscoelastics, whether they had one eye or both eyes done, was a separate entity. So there's been a little bit of a history of using patients as separate entities, as opposed to eyes.

MS. LOCHNER: Right, and I mean, we want to get a feel for clinically how you would assign this correlation factor for all the various variables that you're looking at outcomes.

Now, we, of course, in our guidances, have not addressed this method of potentially using the second eye, and so all of our calculations and sample sizes and whatnot are based on independent people, but if we were to allow this approach, we would have to have some sense of what would the panel consider acceptable for how correlated are the two eyes for the various safety outcome variables and

effectiveness outcome variables.

DR. WEISS: Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: Yes, so certainly the approach of calculating it for people is conservative.

MS. LOCHNER: Right.

DR. BANDEEN-ROCHE: That would essentially be it, and so I have a hard time arguing with that, although I know that others would raise we can't afford to waste any data or money or what have you.

So in terms of getting a sense of the correlation, I would think that if you have decent pilot data, that the correlations I'm talking about could be estimated in a straightforward fashion.

DR. WEISS: Could you perhaps have a subset of the first 20 patients, 50 patients, to draw whatever those correlations are to see whether you could then use separate eyes as separate subjects or the same patient with two eyes as separate?

MS. LOCHNER: I mean, my general impression is that for most sponsors, developing this pilot study and determining this correlation -- I mean, I've seen nobody suggest that to us, first of all, and secondly, how would they do it if at the end of the study they want to use both eyes?

But I've never seen it presented. I've never

even seen a suggestion for what this pilot study would be, and in fact probably what we've recommended in terms of the slow phase in to not put eyes at risk for unproven phakic IOLs -- I mean, if they have foreign experience, we do allow them to phase in quicker, but I kind of suspect that given the slow phase in, doing the pilot study, it's going to be complicated. I mean, it's going to take a while for them to gather that information. I'm not sure how many you typically see in a pilot study to establish these correlations.

DR. BANDEEN-ROCHE: And so, you know, certainly I would be perfectly happy with the conservative approach, but my question to the panel, and I have no idea what the answer to this would be, would one expect the data to be so different in these particular studies that a good sense of reasonable correlation could not be obtained from either -- I mean, LASIK data, that's probably ridiculous, but aphakic IOL trials or is there historical data that are similar enough in nature that a reasonable estimate of the correlation of outcomes in a subject could be done?

DR. WEISS: I mean, I always wonder, if this is new technology, I wonder in terms of we heard about if the IOL is too small, it can induce cataract by sitting on the lens. How often is that phenomena happening and is it correlated between the quality of the measurement, a vagary

of that individual and their eye, and is it the quality of the surgery? So I think some of these may be unknown factors.

Dr. Burns?

DR. BURNS: I mean, I'd be happy with the conservative approach, too. I wouldn't be happy with getting the final analysis coming back suddenly treating the eyes as 600 eyes at the end.

MS. LOCHNER: Oh, no. No. That maybe needs to be clarified. In the sample size calculations that we've done, we've recommended 300 individuals, their first eye, and we require that they collect data on the second eye. The second eye data is not combined in with the first. It's just a separate analysis that's provided to the panel that's really more of a confirmation check that the outcomes are holding up in the second eye and giving you a little bit more numbers. But no, we don't combine them into a 600 sample size and improve the precision.

DR. WEISS: Dr. Mathers?

DR. MATHERS: I was just concerned that there was some thought of holding up doing the second eye for the three-year period.

MS. LOCHNER: Oh, no. No.

DR. MATHERS: But if that's not the issue, then you can afford to be conservative in your statistical

approach if that's what you want.

MS. LOCHNER: And I think that basically, without the detail and the sort of clear way you've just presented it today, Dr. Bandeen-Roche, we've basically given this advice to sponsors that, should they want to use the second eye, they need to determine the correlation between the two eyes and relook at their sample sizes.

So I think just getting this out on the table is important, and I think the point that Dr. Weiss made is probably where most of us sit in the FDA of there's some unknown information and how do you determine the correlation? Perhaps a pilot study, but there's just so much unknown, and it's helpful for us to hear you reiterate what we've basically told sponsors is determined on how the two eyes interact.

DR. BANDEEN-ROCHE: And the only thing I would add to that is that at the end of the study, the data itself provides an estimate of the correlation, and that should be accounted for in any analyses of two eyes.

MS. LOCHNER: Right.

DR. WEISS: Dr. Mathers?

DR. MATHERS: We are saying, though, that the data on the second eye will be collected. Is that correct?

MS. LOCHNER: Oh, yes, and will be reported to the panel.

DR. MATHERS: Fine.

MS. LOCHNER: But it will not be combined with the first eye to get a bigger sample size. It will be reported separately.

DR. MATHERS: Yes, that's key.

DR. WEISS: Mr. McCarley?

MR. McCARLEY: Yes, just quickly. What are the ISO standards? What are the requirements in ISO right now?

MS. LOCHNER: Well, again, all the sample sizes were based on a straightforward calculation not taking the second eye into account, so I believe that the ISO is basically asking for 300 individuals as well.

You know, it's a little different with a standard in terms of -- I mean, you still can go to the notified bodies and present whatever you want, but certainly with the FDA, we would allow companies to propose alternate proposals, but taking into account what's been discussed.

DR. WEISS: Thank you very much.

The other question that I wanted to answer, and we would probably need your input on this as well, is the question of sample size. The 300 is what was put forward by the FDA. Of course, it depends very much on the issues that have been discussed by the three panel reviewers, but does anyone have any comments on that 300 number?

Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: Dr. Grimmett was kind enough to hand me a set of analyses yesterday, and I believe they were done at FDA. Are they going to be presented?

MS. LOCHNER: Well, I don't know if now's the right time to bring it up, but we did have a bit of a question about the endothelial cell density discussion that went on earlier, and that is based on some of Dr. Grimmett's questions, we prepared that table, which is a table of different potential rates of cell loss due a phakic IOL in sample size, and also different standard deviations in the measurement.

DR. WEISS: Why don't show it now, because that is probably --

DR. GRIMMETT: Why doesn't Don Calogero just go over some of the salient points?

MS. LOCHNER: And let me just, before he does that, say that from the earlier discussion, we heard the 1,500 cells and we heard that using the actuarial data, and even perhaps backing the age of cataract and calculating different point on. We heard all that, but what we didn't get from the earlier discussion was what rate do you want to be able to detect? And that essentially is what Don will present. I mean, just before giving you a clinical

impression, of course, you have to see what the sample size is. We're talking about what really kind of seems reasonable. It's a combination of your clinical judgement along with the sample size is that translates into you arrive at a rate that seems reasonable.

So Don's passing that out, and I'll let him explain that to you, because we really didn't walk away understanding whether you felt the 2 percent rate that we've set up is reasonable.

DR. HUANG: Can I make a comment? Donna, I think the sample size itself is not just for statistical analysis. It also has to be considered for practical matters. You know, as we mentioned earlier, in some of the aniridia patients, you may not be able to get all those patients, and so you cannot mandate that 300 eyes.

DR. WEISS: This is very relevant to the slide you're about to see.

MS. LOCHNER: And let me also say that the 300 sample size actually didn't originate from the endothelial cell density study. I mean, way back when we started some of studies, it originated from the IOL work and being able to detect low rate of complications, and then, as we developed the statistical analysis for the endothelial cell density, et cetera, it was a reality check to that sample size and it coincided very nicely, but originally we

carried over a lot of the assumptions from aphakic studies in what we wanted to be able to detect in the complication arena.

DR. HUANG: But also the current discussion is really limited to the phakic population, and then we are probably targeting towards a higher myopia patient, and those are patients more difficult to come by as indicated from yesterday. For the wavefront technology, they could only recruit 130 eyes with a -7.

MS. LOCHNER: That's true. However, I think most of the studies that are ongoing in the U.S. go down as low as a diopter. They aren't necessarily limiting -- beyond the initial stages, when some of the preliminary safety data is being gathered, in later stages of the study, they are going down to 1, 2, 3 diopters.

DR. HUANG: But if this were to be limited to the higher myopic patients --

MS. LOCHNER: You wouldn't have the problem you're discussing. Right.

DR. HUANG: Yes.

MR. CALOGERO: Okay. As Donna said, we need some additional guidance in terms of the sample size. The sample size that we have in the document now of approximately 300 subjects is probably powered to detect endothelial cell loss rates of maybe 2 percent and maybe as

low as 1.5 percent, but it's not going to get down to the .9 percent, which was the lower extreme that Dr. Grimmett brought up.

In terms of this document that I passed around, what it looks at is it looks at sort of a true yearly loss. The left column is the yearly loss from .9 percent up to 2 percent, and then the next three columns on the right are the sample size that you need with an observed, allowable rate per year, which is the fourth column, to give you 90 percent confidence that the true rate is up to the yearly loss rate in the lefthand column.

Like in the first one, if you want the true yearly loss rate to .9 percent, if you in your data you have a standard deviation of 10 percent, you would need a sample of 296 subjects, and your allowable observed rate could be as high or as low as .63 to meet that level.

So it becomes important to first get a sense of what the true standard deviation is in this data, and then secondly, to have a sense of what the panel members would like to see in terms of defining a true rate associated with endothelial cell loss for these devices.

I simply generated the numbers, and we'd like some feedback.

DR. WEISS: I think Dr. Grimmett has a question.

DR. GRIMMETT: Drs. McCarey and Edelhauser put forth precision numbers for those, 2 percent and 9 percent, and I want to know how those correlate over the standard deviation numbers.

PARTICIPANT: Put up the slide. Are they the same?

DR. BANDEEN-ROCHE: No, they're not quite. They're not quite, and so as I understand it, the numbers that were presented this morning were essentially the absolute difference in two measurements over the maximum of those two measurements. I read that off of the handout from this morning.

So what that means is the numerator is the difference in two measurements, and so essentially what you need to do with that, each one of them has a variance. Each one of them contributes one of those standard deviations from your table, except it has to be done in terms of variance.

So to make a long story short, the conversion is that the FDA percent standard deviation is the percent variation that was reported this morning divided by the square root of 2, and that division being that in the numerator of the statistic this morning, there were two measurements being subtracted. So if you approximate no correlation between them, they each contribute a variance,

and then take the square root of that because it's a standard deviation, rather than a variance.

So that's where that square root of 2 comes from, and so if you do that, then I just sketched out on a thumbnail sketch what the 5 percent, 10 percent, and 15 percent on the table in front of you corresponds to in terms of what we hearing this morning. So respectively, that would be 7 percent, 14 percent, and 21 percent. That's just multiply by 1.4, the approximation of square root of 2.

One more number would be that if you went down to 3.5 percent on the FDA table, that would correspond to 5 percent in terms of the figures that we were hearing this morning.

DR. GRIMMETT: This is Dr. Grimmett. If I interpret that correctly, that's actually good news, because that means the numbers that were quoted this morning may be achievable because they actually translate into lower standard deviations.

DR. BANDEEN-ROCHE: I interpret it the same way. Yes, and it seems important to me that -- I mean, measurement, good quality of measurement, is where we stand to gain precision and power, and however that can be absolutely pushed for people to up their standards, it's important.

DR. GRIMMETT: Dr. Grimmett again. So in Dr. Edelhauser's best case scenario, though, the 2 percent precision factor could be achieved. Assuming that could be done, then we're talking a standard deviation of just slightly higher than that. For example, 3 percent or something like that, whatever the number is.

DR. BANDEEN-ROCHE: Well, even lower, right? Yes.

DR. BURNS: Excuse me. Just a clarification. That's the precision of the measurement, but not the standard deviation of the population, is it?

DR. BANDEEN-ROCHE: Right, but that's what I understood this to be. We were talking about the precision of the measurement, right? Yes. So that is what appears in the FDA Table 2. Those standard deviations refer to standard deviation of measurement in a single person.

DR. WEISS: So with this information before us and your extra analysis, I'd like some opinions as far as what numbers of subjects we're looking at and what yearly loss.

MR. CALOGERO: Don Calogero. Can I just mention one thing? I believe that data was on the KeraVision rings, and those were sort of low myopia patients. I believe they went up to 3 or 4 diopters. The population that we're looking for with these devices is

going to be higher.

I've actually had my endothelial cell counts taken and I'm 4 diopters without my glasses. It's correct what they're saying. It's very difficult to focus on that green light. I can imagine if you're 8 diopters or 12 diopters. So I suspect in the populations we're actually looking at, that's a very conservative estimate.

DR. BANDEEN-ROCHE: There was a number being cited of 9 percent this morning. I mean, again, just purely interpolating that would put us at about 7.5. I mean, it's in-between the 5 and 10 percent on this table.

MR. CALOGERO: Okay. That's the KeraVision number.

MS. LOCHNER: So I think what Don is saying is that 9 percent figure came from the KeraVision, which puts you in-between the 5 percent standard deviation and the 10 percent. Maybe it would be prudent to go up at least to the 10 percent standard deviation because the population these will be used in will be a much more difficult population than the KeraVision.

DR. BANDEEN-ROCHE: If I could ask one more question, these calculations, were they based on just a three-year minus three-month difference? That's what was being analyzed?

MR. CALOGERO: Yes, yes.

DR. BANDEEN-ROCHE: Because --

MS. LOCHNER: No, they were repeated measures.

DR. BANDEEN-ROCHE: All four measurements?

MS. LOCHNER: Yes, repeated measures, not --

MR. CALOGERO: Okay. As Ashley said, we established linearity with the four measurements, but in terms of this particular calculation --

MS. THORNTON: Don, please speak into the microphone.

MR. CALOGERO: In terms of this particular calculation, it's I believe the three-month value, the 36-month minus the three-month, and then you simply divide by 2.75. The actual method and equation is right in the information that we provided to you. I simply used the equation that's in that document.

DR. BANDEEN-ROCHE: Right, and so certainly I would expect that some precision could be gained by using all four measurements, rather than just the difference between the last and the first, and so that would impact this table.

Go ahead. Interject, interject.

DR. BRADLEY: This is Dr. Bradley. Could somebody clear up for me, the 9 percent that we're talking about from this morning, if I recall the presentation, was the difference that would have to occur in a single eye to

confirm with 100 percent certainty that in fact a change had occurred. Therefore, that was an estimate of the overall range, not the standard deviation in that distribution. Perhaps the speaker from this morning can clarify that.

PARTICIPANT: I agree with what you just said.

DR. BRADLEY: But I think it's being treated here as a standard deviation.

DR. BANDEEN-ROCHE: Well, let me just clarify. So the overall range -- now, let me see if I read the wrong thing off of your handout, but the way that I understood it was two measurements, maximum minus minimum over maximum?

DR. McCAREY: If you're referring to the graph --

DR. WEISS: Can you identify yourself first for the transcript?

DR. McCAREY: My name is McCarey. If you're referring to the 9 percent one, that was simply a subtraction of baseline and three months for each individual.

DR. BANDEEN-ROCHE: Right, but that's an absolute difference.

DR. McCAREY: Yes.

DR. BANDEEN-ROCHE: Yes, and so you can approximate an absolute difference by the square root of

the squared difference, and so in turn -- I admit there are multiple approximations here, but it's not a bad approximation. The square root of the square, then expectation of the square is a variance, and that's how that enters in.

Yes, but I agree. It's worth doing this more carefully than on my thumbnail.

DR. WEISS: So I think we could actually -- I think you've given us the data to look at and try to balance what we're willing to detect as a yearly loss versus what we're willing to balance against as a maximal amount of endothelial cell loss, and then we can choose the numbers we want.

I would ask Dr. Grimmett if this is basically and opinion-type thing at this point, but that's basically all you want right now. So do you have an opinion as far as what you would wish for a yearly loss and an allowable rate?

DR. GRIMMETT: Sure, but I'm taking into account that some of these numbers have largely varied. For example, in the .9 category of the study of 669 patients, to have good accountability over three years is pretty incredible, and which I don't think is really achievable or reasonable.

Keeping that in mind, the higher numbers I

guess at this point are 1.9, 2 percent loss. I would be extremely disappointed and worried if a phakic IOL actually achieved that rate. I think it would indicate that patients would actually develop corneal edema during their lifetime, especially if they need cataract surgery. I would hope that they'd have a lower rate of cell loss.

What would I like to detect versus what is reasonable? Based on the data here, I suppose if we could be at the worst, assure it's not higher than 1.5. I'd still hope it's a little lower than that. I think a 2 percent threshold is too high based on the actuarial tables that I ran.

Even for some of these lower numbers, even the 1 percent, if they have a 250 sample size -- 244 in this example with a 10 percent standard deviation -- you know, they would be allowed to see a rate of .7 to be sure with 90 percent confidence is not higher than 1. You could still determine other factors, just not with this much precision. It's going to be much harder at the lower rates, and then we admit the normal endothelial cell loss rate is .6 percent per year or so. So we have to account for that factor, and then there will be zero differential between what he phakic IOL is actually doing versus normal cell loss rate. The 1.5 is what I'm looking at.

DR. WEISS: So I think perhaps you could say

the 1.5 percent and allowable rate being --

DR. GRIMMETT: Yes, just straight off the table. I mean, once we set the sample size, it's going to lock this in to what their allowable rate is to be sure of a 90 percent confidence is not higher than our threshold.

Given the difference -- for example, let's look at the 1.5 percent category. Given the difference between the smallest number, the 243 sample size, and the unwieldy 542 independent patients over three years, that's a huge number and it would cost probably a fortune to even try to do it.

So I'm still, I think based on statistics and -- I see I was looking at the 15 percent standard deviation. But looking at the statistics and stuff, I think that the sample size that we're actually asking for is somewhere in the neighborhood of 250 or so. That's what it looks like on this table. Whatever the number happens to be, but I think asking for higher precision than that is not reasonable.

DR. WEISS: So I think from what I understand you're saying, yearly loss would somewhat be dependent on the fact that most -- I would also agree. You don't want to ask for than 250 to 300 patients. So that already locks us into what we want our yearly loss to be.

DR. GRIMMETT: My hope is that with the

precision and the careful techniques that Dr. Edelhauser described, if they can actually be implemented with care, is that by lowering the true standard deviation, we'll have much better precision than we would want, and that's got to be hopeful. Controlling technicians is so important to lower that standard deviation to give the power of the study better precision.

DR. WEISS: Dr. Mathers?

DR. MATHERS: And our precision is going to improve with time because as we monitor afterwards, presuming that is the case, then monitoring for a longer period of time improves our data on the loss rate. It's not part of this table, but this doesn't get worse over time. It gets better if you continue to monitor.

DR. WEISS: Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: Yes, I would just like to bring up a little something about the safety and effectiveness precision given a sample size of 300. This was Attachment A, Section A.1, and by my calculation -- you know, of course, zero events is the least that you can have -- with a sample size of 300, that gave a 95 percent upper confidence bound of .01.

Now, so that's a 1 percent, say, adverse event rate, and I would just submit that for the panel's consideration. I don't think that that can be argued as

meeting the .001 standard that was cited in the attachment in the way that I feel is honest and candid.

DR. WEISS: What sample size would allow you that rate?

DR. BANDEEN-ROCHE: Well, unfortunately, it's very large.

DR. WEISS: Well, what is very large?

DR. BANDEEN-ROCHE: Three-thousand.

DR. WEISS: So in other words, we have to change the rate. We might want that rate, but none of us believe that a study with 3,000 patients can be done.

DR. BANDEEN-ROCHE: That's right, but maybe it just supports the importance of postmarketing data.

DR. WEISS: Okay. So it supports our concern for stringency.

Dr. Bullimore?

DR. BULLIMORE: And one of the continuing limitations of the data we consider is we're presented, bombarded, with event rates and, give complication rates or adverse event rates, we choose to ignore the confidence intervals or we're not presented with the confidence intervals that you give you an indication of the precision of those estimates, and if you really truly want to ensure that the event rate is, say, less than 1 percent, you would have to do as Dr. Bandeen-Roche suggested, enroll

considerably more patients, as was done, say, in recent continuous wear contact lens studies.

We choose to ignore information, we sort of try and meet targets, and we keep in the back of our minds often what the precision of the estimate might be, but it's not something we consider on a regular basis, and maybe we should, but I'm not sure that we'd like the answer that we'd get if we were presented with those on a regular basis.

DR. WEISS: Dr. Bandeen-Roche?

DR. BANDEEN-ROCHE: Well, just stating it another way, I mean, is the panel willing to live with 5 percent of studies claiming an event rate of .001 or less when in fact it's higher than 1 percent? I mean, that's the ramification.

DR. WEISS: I think the difficulty is in the real world, if we required the number of patients we would like to get the answer, it would take so many years by that point the technology would be archaic.

Mr. McCarley?

MR. McCARLEY: Just one comment. There is always an ongoing postmarket surveillance on products. Every year we have an annual report in all products, and especially implants, where we essentially divide the number of adverse events we've had by the number of implants that

have taken place. So if we saw any increase in it, the FDA would immediately take action or we'd have to justify why that would be.

So I agree for the purpose of making an initial decision for a PMA, you might not have all the information, but you certainly have the mechanism in place to continue to monitor any higher rates.

DR. WEISS: Dr. Grimmett?

DR. GRIMMETT: Dr. Grimmett. I would counter that by saying that postapproval, there is probably significant underreporting of adverse events.

DR. MATOBA: We're going to collect data on both eyes, right? So for events, specific events, that would become available to the FDA, wouldn't it? On twice as many eyes potentially as 300?

MS. LOCHNER: Right, but the statistical assumptions that, for example, would be inherent in this table would then have to be adjusted.

DR. MATOBA: From a practical point of view, but in terms of missing something terrible, it's not as bad as she says.

MS. LOCHNER: I think from a practical standpoint, I hear you. I mean, you will have more eyes from a practical standpoint.

But I think the issue with phakic IOLs isn't

missing something catastrophic early on, but missing a slow bleed that's occurring over time and approving it without understanding that the rates could be higher.

DR. WEISS: Dr. Bullimore?

DR. BULLIMORE: Reasonable assurance of safety. That's what we're asked for.

DR. WEISS: I guess that's the difference between the 300 and the 3,000.

DR. BULLIMORE: Exactly.

I have one other issue on the endothelial cell count which I've hinted at before and I'll come back to. When these data are presented, I think it will be appropriate not only to have the mean rate of loss, whether you give that annually, but I think over a three-period, knowing the proportion of eyes that have lost 10 percent, 20 percent, and 30 percent of endothelial cells -- I mean, I'm sure a reviewer's going to ask for that information, but prospectively it should be at the forefront of the analyses.

DR. WEISS: I wanted to find out if the agency had any other questions for the panel at this point.

MS. LOCHNER: No, just if there are any other comments on any other sections of the guidance.

One of the things that I think I took away from the earlier discussion on contrast sensitivity is that we

may need to provide to vision scientists some of the data upon which we came to this conclusion about contrast sensitivity, and so we may follow up with a homework assignment to look at that because it's possible, first of all, that we're misinterpreting what we're looking at, and so we took those contrast acuity comments especially to heart if we are in fact doing that.

DR. WEISS: Dr. Matoba had a comment.

DR. MATOBA: I had a question about the guidance. Number 5, study population. This is phakic IOLs for myopes, specified minimum uncorrected visual acuity 20/40 or worse, meaning you could have myopia uncorrected visual acuity of 20/40 and then be eligible to get into the myopic phakic IOL study? Twenty/forty doesn't seem compatible with high myopia.

DR. EYDELMAN: Dr. Eydelman. This is for all phakic IOLs. As Donna has mentioned previously, current studies are not limited to high myopia. So we have phakic IOLs for -2 and -3.

DR. WEISS: So would any members -- and I'm going to regret asking this question.

(Laughter.)

DR. WEISS: Briefly, would any members of the panel -- or actually, even more importantly, does the FDA care whether the panel wants it to be 20/40 or not or it's

irrelevant?

MS. LOCHNER: We care.

DR. WEISS: You care. That's too bad.

(Laughter.)

DR. WEISS: So do any members of the panel have any disagreement with doing a phakic IOL for someone who's 20/40?

DR. BULLIMORE: I'm having a senior moment. You were talking about excluding patients with entering visual acuity of worse than 20/40?

DR. WEISS: Twenty/forty uncorrected. It's uncorrected visual acuity of 20/40. I want my 20/40 --

DR. MATOBA: Would make you eligible to get in the study.

DR. WEISS: Would make you eligible to have a phakic IOL at this point.

DR. GRIMMETT: This is Dr. Grimmett. You're using the 20/40 as a marker for your refractive error.

DR. WEISS: It's about a -1, isn't it?

DR. GRIMMETT: Yes. You're really asking the question should patients with low myopic or low refractive errors be entered into trials that have significant risks that we've discussed today of cataracts, endothelial cell loss, pigment dispersion, glaucoma, et cetera?

DR. WEISS: And at the present time, they are

being entered into this.

Dr. Mathers?

DR. MATHERS: I think they should not be entered into this study. We should have a cutoff that is much higher than that for patients to enter the study.

DR. WEISS: Okay. So what would your cutoff be?

DR. MATHERS: Minus 8.

DR. WEISS: That's pretty high.

DR. MATHERS: Maybe -6. I mean, -6 is very treatable with most LASIK procedures.

DR. WEISS: So you would come down to a -6.

DR. MATHERS: Yes.

DR. WEISS: Dr. Swanson, do you have an opinion on this?

DR. SWANSON: Well, I have an opinion on most things, but I agree that we're talking about something that has -- we want to determine what the risks are, so it makes sense to look at the population that's supposedly to be served by this risky procedure.

DR. BULLIMORE: I have a question related to the question. I think if we start prefacing entry criteria and say, well, this population can be adequately served by other technology, we're actually entering a very dangerous bias zone.

A question for the folks who do this kind of thing. In terms of the safety of the device, are there any a priori reasons why endothelial cell count, contrast sensitivity loss, and lens opacifications would expect to be greater in a low myope compared to a high myope or vice versa?

DR. WEISS: I don't think they would be, but I think the concern is why make the cutoff at 20/40? Why not do it at 20/25?

DR. BULLIMORE: Yes. Well, I agree that -1 is perhaps a little too conservative, but I don't think we should say, well, we approved LASIK up to -6. That should be our cutoff.

DR. WEISS: You know what? I think what you're hearing, and obviously this discussion could go on for a while, but I think some members of the panel have a concern that the low myopes, the risk/benefit ratio might not be the same as in the high myopes, and where you would draw that line would be up to discussion. Perhaps it would it be appropriate for these IDEs to first do a higher group of myopes, and when there is proven to be some sort of clinical safety and efficacy, then expand the trial to the lower myopes.

Dr. Eydelman?

DR. EYDELMAN: Malvina Eydelman. That is

exactly what I was trying to make a point of, that we usually allow brand new phakic IOLs only in the higher degrees of myopia, and once the sponsor obtains enough safety information on the high myopes and submits it to FDA, then internally we review it and decide that is sufficient, and we allow lower ranges. Again, depending on safe we assess it to be, that's the degree of myopia that we allow it to go down to.

DR. WEISS: Mr. McCarley?

MR. McCARLEY: Just very quickly, I agree with it. I think that it's prudent to study higher myopes, develop a level of confidence and safety, and then move down, but I would ask I guess a question about LASIK, another refractive technology that apparently is now safe and effective, though from what we heard yesterday morning or at the beginning of this session, it may not be completely true when you have large numbers of patients.

Aren't there lasers approved right now for -15, for instance? I think so.

DR. WEISS: There are, but I don't think they're being used for it.

MR. McCARLEY: They're approved for it. That's what I'm saying. So it's sort of a double standard and I agree we all think of phakic intraocular lenses as treating high myopia, and in fact, if you look at the means of the

data that's presented at the American Academy of Ophthalmology and ASCRS, you'll see that that's up around the 12, 13.

But in fact, this may be a replacement technology. There may be benefits we don't know over LASIK.

DR. WEISS: Dr. Swanson?

DR. SWANSON: Good. Thanks. I've been promoted.

Well, I think the one question to consider there is, in terms of effectiveness, one of the effectiveness criteria is percentage of eyes that achieve uncorrected visual acuity of 20/40 or better. So if there are a lot of people enrolled that are just worse than -- that are 20/50, that effectiveness is not going to mean as much. So that's something in terms of study design. The safety may not be different across eyes, but the effectiveness should be considered.

DR. WEISS: Does the agency have any other questions?

(No response.)

DR. WEISS: I want to thank the panel and the presenters and the agency for all their work and excellent preparation, and Sally will have some closing comments before we end the meeting.

MS. THORNTON: I, too, would like to add my thanks to the panel, and to Drs. Werner, Edelhauser, and McCarey for being with us today. It's been quite a contribution you've given to our proceedings, and I thank the panel for all their hard work for yesterday as well.

I will be letting you know about mid-September what the story is for the November 14-15 tentative panel meeting schedule. So stay in touch with your website.

DR. WEISS: The meeting is closed.

(Whereupon, at 2:03 p.m., the meeting was adjourned.)